

Translation

PATENT COOPERATION TREATY

PCT/EP2003/006866



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT1885-00983jk	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP2003/006866	International filing date (day/month/year) 27 June 2003 (27.06.2003)	Priority date (day/month/year) 03 July 2002 (03.07.2002)
International Patent Classification (IPC) or national classification and IPC C07D 489/08		
Applicant ALCASYNN PHARMACEUTICALS GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 03 February 2004 (03.02.2004)	Date of completion of this report 06 September 2004 (06.09.2004)
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

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I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☐ the international application as originally filed.

☒ the description, pages 1-103, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☐ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-15, filed with the letter of 06 August 2004 (06.08.2004),
Nos. _____, filed with the letter of _____.

☐ the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☒ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☒ complied with.
- ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. _____

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-15	YES
	Claims		NO
Inventive step (IS)	Claims	1-15	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-15	YES
	Claims		NO

2. Citations and explanations

The assessment of the present application is based on the following search report citations:

- D1: CHENG, C. Y. ET AL.: "N-Cubylmethyl Substituted Morphinoids as Novel Narcotic Antagonists" BIOORGANIC & MEDICINAL CHEMISTRY, Vol. 4, No. 1, 1996, pages 73-80
- D2: GB-A-1 300 419 (BUCKETT, W.R.; BOSMAN, H.H.) 20 December 1972
- D3: EP-A-0 250 796 (DU PONT) 7 January 1988
- D4: COOP, A. ET AL.: "Delta Opioid Binding Selectivity of 3-Ether Analogs of Naltrindole" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, Vol. 9, 1999, pages 3435-3438,
- D5: SCHÜTZ, J. ET AL.: "Synthesis and Biological Evaluation of 14-Alkoxymorphinans. 17. Highly delta Opioid Receptor Selective 14-Alkoxy-Substituted Indolo- and Benzofuromorphinans" J. MED. CHEM., Vol. 45, 2002, pages 5378-5383.

Whether document D5 should be taken into consideration for the assessment of the present application in the national / European phase depends on the validity of the

corresponding priority.

- D6: US-A-4 272 540 (RAZDAN RAJ K ET AL) 9 June 1981
- D7: SCHMIDHAMMER H ET AL: "SYNTHESIS AND BIOLOGICAL EVALUATION OF 14-ALKOXYMORPHINANS. 1.HIGHLY POTENT OPIOID AGONISTS IN THE SERIES OF (-)-14-METHOXY-N-METHYLMORPHINAN-6-ONES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, Vol. 27, No. 12, 1984, pages 1575-1579
- D8: DE 34 12 727 A (SCHMIDHAMMER HELMUT DR) 17 October 1985
- D9: KLEIN P ET AL: "O3-(2-Carbomethoxyallyl) ethers of opioid ligands derived from oxymorphone, naltrexone, etorphine, diprenorphine, norbinaltorphimine, and naltrindole. Unexpected O3-dealkylation in the opioid radioligand displacement assay" JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, Vol. 35, No. 24, 1992, pages 4589-4594
- D10: PORTOGHESE P S ET AL: "Synthesis of naltrexone-derived delta-opioid antagonists. Role of conformation of the delta address moiety" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, Vol. 37., No. 5, 1994, pages 579-585
- D11: EP-A-0 030 685 (SISA INC) 24 June 1981
- D12: US-A-4 390 699 (BROSSI ARNOLD ET AL) 28 June 1983
- D13: US-A-4 912 114 (REVESZ LASZLO) 27 March 1990.

The present application concerns morphinan derivatives of the formulas (I) and (Ia) and pharmologically compatible salts of the formulas (IA) and (IAa) derived therefrom. The problem to be solved by the application is understood to be that of providing further morphinan derivatives with analgesic action.

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The claims were modified in such a way that R_2 is no longer defined as a hydrogen and hence position 14 no longer encompasses an OH group. Furthermore, sulphur and CH_2 have been excluded as possibilities for the variable X. In the light of these changes, the claimed subject matter is novel over the cited prior art. The salts claimed in claim 2 continue to differ from the prior art in that two organic groups and no hydrogen are bonded to the nitrogen (D3).

Claims 1-15 meet the requirements of PCT Article 33(2).

The experimental data on receptor affinity and analgesia provided in the description prove that the disclosed groups of compounds achieve the stated object and, in part, are considerably more effective than those of the prior art (PCT Article 33(3)).